As such, a further aspect of the composition of the present invention is the ***acidic buffering potential*** in physiological solutions. More particularly, when the composition of the present invention ***is put into a solution***, such as a bodily fluid at physiological pH (e.g. in an *in vivo* application) or another weakly basic solution, the composition ***acts to buffer the solution at an acidic pH (i.e., the pH of the composition is less than 7)***. Additionally, if the composition is implanted into a mammal, the composition can buffer the surrounding microenvironment to an acidic pH. More particularly, the present components can buffer such solutions in the immediate environment to a pH between about 4 and about 7, more preferably between about 5 and about 6.8, and most preferably between about 5.5 and about 6.7.

Specification at page 11 lines 8-23.

Applicants submit that the foregoing disclosure makes it clear that the term "acidic buffering potential" means that the composition, when placed in a solution that is initially at physiological pH, buffers the solution to an acidic pH, and that when implanted into a patient, buffers the immediate environment near the composition to an acidic pH. Accordingly, Applicants respectfully maintain claim 1 and submit that it is not indefinite under .S.C. §112, second paragraph.

Claims 1-8 and 10 further stand rejected under 35 U.S.C. §112, first paragraph, as not enabling for a composition which has an acidic buffering potential in physiological pH. Office Action at page 4 lines 1-4. The Examiner asserts that Applicants in the specification have merely "speculated that the composition of the present invention will increase the acidity of the physiological area around the composition due to the acidic nature of the calcium phosphate compounds." Office Action at page 5 lines 10-12. The Examiner further takes the position that "it has not been shown in the Instant specification wherein the composition of the Instant claims actually decreases physiological pH." Office Action at page 5 lines 14-16. Applicant respectfully traverses these bases of rejection.

Applicants respectfully submit that the instant application is fully enabling for the claimed inventions. First, it is not "speculation" that the compositions will buffer a physiological solution or surgical microenvironment to an acidic pH. Applicants respectfully submit that persons of skill in the art would be familiar with acidic and basic buffer salts, particularly acidic and basic calcium phosphate salts, and would understand that such salts indeed have an effect on pH. Where Applicants invention departs from the prior art is not its use of acidic buffer salts *per se*, but in providing such salts so as to ***ensure an acidic pH environment*** to enhance the activity of the bone growth factor. Provided with the instant disclosure, persons of skill in the art would readily be enabled to replicate the claimed inventions.

Enablement is particularly clear in light of the literally dozens, if not hundreds, of experiments on laboratory rats represented by the data in Figures 2-10. In this regards, Applicants wish to clarify what appears to be a misconception inherent in the Examiner's statement that "Applicants' only working example was carried out using Ostite." Office Action at page 6 lines 2-3. To the contrary, the Ostite example was only used to provide a representative example of how to make implant using calcium phosphate salts. Samples using other calcium phosphate salts—whether acidic, neutral or basic—can be, and in this instance were, made using substantially the procedure outlined for Ostite. Other techniques of making calcium phosphate salt compositions are known in the art. See, e.g., Ohura at pages 168-169 (describing preparation of an implant using β-tricalcium phosphate ("β-TCP") and monocalcium phosphate monohydrate). The difficulty in achieving the present inventions lies not with the intricacies of preparing compounds comprising calcium phosphate salts, but in the failure of the prior art to appreciate that by using such salts having an acidic buffering capacity as opposed to neutral or basic buffering capacities, the activity of bone growth proteins can be enhanced.

The Examiner has not considered the large amount of data provided in Figures 2-10, which validate and support the claims under consideration. These figures report explant masses, histology scores, mineral concentration, and mineral mass for sample disks comprising numerous calcium phosphate salts of various acidic and basic buffering capacities. The benefits flowing from the use of more acidic calcium phosphate compounds are clear from these figures. Accordingly, it is respectfully Applicants' position that the claims under consideration are fully enabled by the specification, and that this rejection should be withdrawn.

II. Rejections under 35 U.S.C. § 102

Claims 1-5, 8, and 10 stand rejected under 35 U.S.C. §102(b) as anticipated by Ohura et al., *J. Biomed. Mater. Res.* 44(2):168-175 (1999) (hereinafter "Ohura"). Specifically, the Examiner alleges that Ohura, which discloses a bone cement comprising comprising β-tricalcium phosphate ("TCP"), monocalcium phosphate monohydrate ("MCPM"), and recombinant human bone morphogenetic protein-2 ("rhBMP-2:"), anticipates the claimed invention. Office Action at page 7 line 16 – page 8 line 10. Applicants respectfully traverse this rejection.

There is no teaching or suggestion whatsoever in Ohura of a composition having an acidic buffering potential, or the capacity of buffering a solution at physiological pH to an acidic pH. The Examiner's reliance on Ohura's use of MCPM is misplaced. MCPM comprises only 7.1% of the Ohura cement mixture. TCP, a neutral pH calcium phosphate salt, comprises 44.5% of the mixture, and would predominate in determining the pH effects of the Ohura composition. Further, there is nothing in Ohura to suggest that pH effects are even considered significant, much less provide an affirmative teaching to provide an acidic pH against the prevailing wisdom in the art.

Applicants note for the record that the instant claims are not directed to any and all bone growth mixtures comprising an acidic calcium phosphate salt, but rather such compositions having an acidic buffering capacity. As noted in the specification, hydroxyapatite is the most commonly used form of calcium phosphate, because it most closely approximates the mineral content of actual bone tissue. Specification at page 2 lines 20-23. To obtain hydroxyapatite *in vivo*, many cement manufacturers incorporate both a highly basic calcium phosphate salt and an acidic calcium phosphate salt into the cement, which then precipitates hydroxyapatite at a slightly basic pH. Such cements do not, however, provide an acidic buffering capacity, and indeed most frequently provide the basic pH of hydroxyapatite. This is fundamentally different from the present invention.

Ohura also fails to disclose a substrate as required by the claims. The present specification clearly defines the substrate of the present claims as a component that provides a structure for the other components of the composition, namely the bone protein and the calcium and/or phosphate sources. Ohura's calcium phosphate compounds are calcium and/or phosphate sources, and thus, Ohura would require a further substrate to disclose every element of the present claims. Therefore, the present claims are not anticipated by Ohura, and this rejection should be withdrawn.

III. Rejections under 35 U.S.C. § 103

Claims 1-8 and 10 first stand rejected under 35 U.S.C. §103(a) as obvious over Kwan et al., U.S. Pat. No. 6,187,047 B1 (hereinafter "Kwan") in view of Constantz, U.S. Pat. No. 5,047,031 (hereinafter "Constantz"). Specifically, the Examiner states that Kwan describes artificial bone matrices comprising a collagen substrate, calcium phosphate cements, and added proteins. The Examiner points to Constantz as teaching acidic calcium phosphate compositions as suitable artificial bone matrices and alleges these acidic calcium phosphates can be used in the compositions of Kwan. Applicants respectfully traverse this rejection.

Constantz states several different minerals can be prepared, depending on the ratio of calcium to phosphate ion, including brushite (1:1 Ca:P), octacalcium phosphate (1.33:1 Ca:P), tricalcium phosphate (1.5:1 Ca:P), and hydroxyapatite (1.67:1 Ca:P) (col. 4, lines 56-67). In terms of the present specification, at page 13, lines 3-13, these compounds have, in the formula $xCaO{\cdot}P_2O_5$, values of x of 2, 2.67, 3, and 3.33, respectively. From the present specification, one of ordinary skill in the art would consider at least tricalcium phosphate and hydroxyapatite, and possibly octacalcium phosphate as well, to not lower the pH of a physiological solution to below 7. As already noted above, Applicants do not claim all compositions comprising an acidic calcium phosphate salt, but only those having an acidic buffering capacity or the capability of providing an acidic pH to a solution. In this regard, the fact that Constantz calls for the neutralization of phosphoric acid (col. 5, lines 31-52) suggests avoiding acidic buffering capacities. This is consistent with the fact that Constanz considers hydroxyapatite to be a preferred component (col. 5, lines 54-55).

In sum, neither Constantz nor Kwan recognizes the importance of an acidic composition in enhancing the activity of bone growth proteins, and thus, there is no motivation to combine these references. Even assuming, arguendo, that such a combination were made, it would not guide persons of skill in the art to provide compositions having an acidic buffering capacity according to the present invention. Therefore, the present claims are patentable over Kwan in view of Constantz, and this rejection of claims 1-8 and 10 should be withdrawn.

Claims 1-8 and 10 also stand rejected under 35 U.S.C. §103(a) as obvious over Ohura in view of Kwan. According to the Examiner, Kwan teaches a collagen substrate for calcium phosphate cements which can be used with the calcium phosphate cements of Ohura. Applicants respectfully traverse this rejection.

As already noted, Ohura provides no teaching or suggestion to provide compositions having an acidic buffering capacity. Therefore, the use of the calcium phosphate cement of Ohura in the compositions of Kwan, or the collagen of Kwan in the compositions of Ohura, would not be expected to lower the pH of a physiological solution in which the compositions would be put to below 7. Therefore, the present claims are patentable over Ohura in view of Kwan, and this rejection of claims 1-8 and 10 should be withdrawn.

IV. Conclusion

Applicant respectfully submits that the claims as amended are allowable over the prior art of record. Accordingly, it is requested that the proposed Amendment be entered and that a Notice of Allowance be issued.

Nov. 18, 2002
Date

Respectfully submitted,

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APPENDIX A

CLAIMS MARKED-UP TO SHOW CHANGES MADE

2. (Amended) A bone growth composition, comprising:

(a) a substrate;

(b) a bone growth protein; and,

(c) a [source of] salt composition consisting essentially of an acidic calcium phosphate salt,

wherein [said] the bone growth composition has an acidic buffering potential in physiological solution.

3. (Amended) A bone growth composition for implantation into a mammal, comprising:

(a) a substrate;

(b) a bone growth protein; and,

(c) a [source of] salt composition consisting essentially of one or more acidic calcium phosphate salts,

wherein the [said] composition, when implanted into a mammal, buffers the immediate physiological environment around the composition to a pH between about 4 and about 7 [has an acidic buffering potential in physiological solution].

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